
Indian hedgehog regulates intestinal stem cell fate through epithelial-mesenchymal interactions during development.

Journal: Gastroenterology

Publication Year: 2010

Authors: Cynthia Kosinski, Daniel E Stange, Chuanrui Xu, Annie Sy Chan, Coral Ho, Siu Tsan Yuen, Randy C Mifflin, Don W Powell, Hans Clevers, Suet Yi Leung, Xin Chen

PubMed link: 20542037

Funding Grants: Training Grant I

Public Summary:

Scientific Abstract:

BACKGROUND & AIMS: Intestinal stem cells (ISCs) are regulated by the mesenchymal environment via physical interaction and diffusible factors. We examined the role of Indian hedgehog (Ihh) in mesenchymal organization and the mechanisms by which perturbations in epithelial-mesenchymal interactions affect ISC fate. **METHODS:** We generated mice with intestinal epithelial-specific disruption of Ihh. Gross and microscopic anatomical changes were determined using histologic, immunohistochemical, and in situ hybridization analyses. Molecular mechanisms were elucidated by expression profiling and in vitro analyses. **RESULTS:** Deletion of intestinal epithelial Ihh disrupted the intestinal mesenchymal architecture, demonstrated by loss of the muscularis mucosae, deterioration of the extracellular matrix, and reductions in numbers of crypt myofibroblasts. Concurrently, the epithelial compartment had increased Wnt signaling, disturbed crypt polarity and architecture, defective enterocyte differentiation, and increased and ectopic proliferation that was accompanied by increased numbers of ISCs. Mechanistic studies revealed that Hh inhibition deregulates bone morphogenetic protein signaling, increases matrix metalloproteinase levels, and disrupts extracellular matrix proteins, fostering a proliferative environment for ISCs and progenitor cells. **CONCLUSIONS:** Ihh regulates ISC self-renewal and differentiation. Intestinal epithelial Ihh signals to the mesenchymal compartment to regulate formation and proliferation of mesenchymal cells, which in turn affect epithelial proliferation and differentiation. These findings provide a basis for analyses of the role of the muscularis mucosae in ISC regulation.

Source URL: <https://www.cirm.ca.gov/about-cirm/publications/indian-hedgehog-regulates-intestinal-stem-cell-fate-through-epithelial>